REMARKS

Claims 1-3, 4, 6-11, 13-15, and 37-47 were pending. Claim 4 has been rewritten to be in independent form. Upon entry of the amendment claims 1, 3, 4, 6-11, 13-15, and 37-47 will be pending.

No new matter has been entered.

Interview Summary

Applicants thank Examiner Fredman and Examiner Calamita for participating in a telephonic interview on June 30, 2005 where the rejections of the claims were discussed. Applicants have considered the issues discussed and incorporated elements of the issues discussed within this response.

Rejections under 35 U.S.C. § 112, first paragraph

The Office has maintained the rejection of claims 4 and 40 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The Office alleges that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Office alleges that the claims contain new matter. Applicants respectfully disagree.

In the previous response to the new matter rejection Applicants submitted a declaration by Dr. Scott A Waldman pursuant to 37 C.F.R § 1.132. The declaration clearly states:

> The markers that are listed in Claims 4 and 40 are known to be epithelial cell markers. Furthermore, one of ordinary skill in the art would know that the markers listed in Claims 4 and 40 are epithelial cell markers.

(Declaration, p.1, filed with previous response on July 7, 2004) Although all the markers listed in claims 4 and 40 are not specifically identified in the specification as epithelial cell markers, the markers themselves are inherently epithelial cell markers. One of ordinary skill in the art would know that the listed markers are epithelial cell markers.

In response to this evidence (declaration) the Office states:

> Applicant provided no evidence (i.e. published journal articles) with the declaration to support the assertion that the specified markers are inherently epithelial cell markers and these markers are well known as epithelial cell markers to those of skill in the art. The new matter rejection is therefore hereby maintained.

(Office Action, page 11). Applicants respectfully urge that the Office has not properly considered the declaration. When the declaration is given its proper weight the rejection should be withdrawn.

The M.P.E.P. is instructive on how declarations submitted as evidence should be handled.

> (B) Consideration of evidence...Where the evidence is insufficient to overcome the rejection, the examiner must specifically explain why the evidence is insufficient. General statements such as "the declaration lacks technical validity" or "the evidence is not commensurate with the scope of the claims" without an explanation supporting such findings are insufficient.

(M.P.E.P. § 716.01). The Office has done what the M.P.E.P. clearly states is insufficient. The Office's only rebuttal is that the declaration did not have any published journal articles to support the statements contained therein. It is well settled that a statement in a declaration submitted under 37 C.F.R § 1.132 is considered fact. In *In re Alton* (76 F.3d 1168; 37 U.S.P.Q.2D (BNA) 1578) the court held that it was an error for the examiner to dismiss a declaration without an "adequate explanation of why the declaration failed to rebut" the rejection. (*Id.* at 1174). The CAFC also stated that a "***declaration is offering factual evidence*** in an attempt to explain why one of ordinary skill in the art would have understood the specification..." (*Id.*, emphasis added) The declaration submitted by Dr. Waldman is a statement of fact about the inherent properties of the markers listed in claims 4 and 40. This statement of fact can only be dismissed as insufficient if the Office specifically explains why the statements in the declaration are not correct. The Office is not allowed to dismiss the statements as insufficient without a thorough explanation, which the Office has failed to provide. Without an adequate explanation the Office must withdraw the rejection.

Therefore, because the declaration was not considered properly and the declaration provides facts about the markers listed in claims 4 and 40 that have not been rebutted by the Office, the claims do not introduce new matter. In view of the foregoing, Applicants respectfully request that the rejection be withdrawn.

The Office has maintained the rejection of claims 1-4, 6-11, 13-15 and 37-47 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The Office alleges that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Office further alleges that the genus encompassed by the claims

> comprises the class of compounds (mRNAs) that share a function (encoding a disseminated epithelial cell marker, wherein the marker is a differentiation-specific antigen). However, the specification does not specify a common structure of this class of mRNAs. That is, while the members of the genus encompassed by the claims...share a function, they do not share a structure that is similar. Each mRNA encompassed by the genus will have different structure, absent any disclosed structural similarities provided by the specification. That is, even assuming, the mRNAs encompassed by the genus are functionally similar, they are not structurally similar, and therefore, the functional description of the mRNAs does not provide adequate written description to the plurality of other structurally distinct mRNAs that are encompassed by the claimed invention.

(Office Action, page 4). Applicants respectfully disagree.

Applicants provided a similar response to this rejection in response to the non-Final Office Action that preceded the present action. Applicants, however, believe that the response is worth repeating because the rejection is improper.

The M.P.E.P. states,

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice (see i)(A), above), reduction to drawings (see

> i)(B), above), or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see i)(C), above). See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

(M.P.E.P.§ 2163).

The Office alleges that Applicants have only described "eight epithelial cell markers". (Office Action, page 5). However, Applicants have described over 3 times that number (see, for example, the 26 markers listed in claim 4). Therefore, Applicants have described a representative number of species of the genus.

> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

(M.P.E.P § 2163). Although, the mRNA sequence of each marker is different, each sequence is a nucleic acid molecule and therefore share a common structural component (ribose backbone). Applicants have described a variety of the species that "reflect the variation within the genus." The Office further alleges that the "specification does not describe which mRNA are specific for a particular tissue-specific marker." (Office Action, page 5). Applicants are not required to describe every member of a genus as the Office alleges. Rather, the skilled artisan would know other tissue-markers that can be used as disseminated epithelial markers. The present invention provides a method for eliminating illegitimate transcription by eliminating CD34+ cells and then using the remaining population of cells to detect the mRNA of a disseminated epithelial marker. The exact marker that is used is not necessary to show possession of the invention at the time the application was filed. Applicants have provided numerous examples of disseminated epithelial markers, but the skilled artisans can use any disseminated epithelial marker of their choosing. As discussed above, the specification defines a disseminated marker as referring to "a gene product associated with a particular cell or tissue type that may serve as an indication that a cell has become disseminated from its site of origin or normal location in the body." One of skill in the art knows and can

determine if a gene product is associated with a particular cell or tissue type. One of skill in the art would clearly understand that Applicants have described the characteristics and features of a "disseminated epithelial marker." Thus, Applicants were clearly in possession of the genus at the time the application was filed.

In view of the foregoing, Applicants respectfully request that the rejections under 35 U.S.C. § 112 be withdrawn.

Rejections under 35 U.S.C. § 102

Claims 1-4, 7-11, and 13 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Zippelius *et al.* (Journal of Clinical Oncology (1997) 15(7):2701-2708, hereinafter "Zippelius"). The Office alleges that Zippelius discuses methods of detecting the presence of a disseminated epithelial cell marker comprising the steps of: eliminating CD34+ cells from the sample and detecting the presence of mRNA that encodes the marker, wherein the marker is a differentiation-specific antigen. The Office states

> It is noted that the removal of mononuclear cells before RT-PCR meets the limitation of "eliminating CD34+ cells", since mononuclear cells from bone marrow will contain CD34+ cells. Furthermore, the claims are drawn to "eliminating CD34+ cells", which can be interpreted as only eliminating a fraction of mononuclear cells.

(Office Action, page 6). Applicants respectfully disagree.

For a reference to anticipate a claim each and every element as set forth in the claim must be found either expressly or inherently described in a single prior art reference. An anticipation rejection requires a showing that each limitation of a claim be found in a single reference. *Atlas Powder Co. v. E.I. DuPont de Nemours & Co.*, 224 U.S.P.Q. 409, 411 (Fed. Cir. 1984).

Claims 1-4, 7-11, and 13 are not anticipated by Zippelius because the reference does not describe either expressly or inherently every element of the claims. Claim 1 states

> A method of detecting the presence of a disseminated epithelial cell marker in a sample comprising the steps of
>
> a) eliminating CD34+ cells from the sample; and

> b) detecting the presence of mRNA that encodes the marker; wherein the marker is a differentiation specific antigen;
>
> wherein said detection of said mRNA indicates the presence of a disseminated epithelial cell marker.

The Office alleges that Zippelius removes mononuclear cells before performing RT-PCR. However, Applicants respectfully assert that the Office has misinterpreted the reference. Zippelius states

> BM [bone marrow] was aspirated...The volumes aspirated varied from 6 to 10 mL which yielded between $6X10^6$ to $5X10^7$ mononuclear cells (MNC). ***MNC were isolated by density-gradient centrifugation...A fraction of these cells were removed for RT-PCR analyses***, and the remaining cells were deposited onto glass slides by cytocentrifugation at 150 x g for 8 minutes.

(Zippelius, p. 2702, left column, lines 13-21, emphasis added). Zippelius detects a mRNA molecule by RT-PCR in a sample that has been ***enriched*** for mononuclear cells, which includes CD34+ cells, not in the sample from which the cells have been removed. Thus, Zippelius has not eliminated CD34+ cells, rather Zippelius enriched the sample for the mononuclear cells and performed RT-PCR on the mononuclear cells. Accordingly Zippelius fails to anticipate claims 1 and 4. Zippelius also fails to anticipate the claims that depend from the independent claims, which are not anticipated by Zippelius.

In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 102 be withdrawn.

Rejections under 35 U.S.C. § 103

Claims 1-4, 7-11, 13, 37-40, and 42-45 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Ts'o et al (U.S. Patent No. 5,962,237), in view of Palsson, B. (U.S. Patent No. 5,874,266). The Office alleges that Ts'o discusses methods of isolating and enriching rare cells from body fluids by negative selection of non-tumor cells such as white blood cells from the CD family. However, as the Office points out Ts'o fails to teach the removal of CD34+ cells. The Office alleges that Palsson discusses that eliminating CD34+ cells from tumor cells is advantageous to ensure isolation of only the

tumor cells and that negative CD34+ selection can be used in conjunction with detection of epithelial cell markers. The Office alleges that

> in view of the teachings of Palsson, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Ts'o so as to have eliminated CD34+ cells from rare cancer cells. One of ordinary skill in the art would have been motivated to modify the method of Ts'o to have eliminated CD34+ cells, in order to have achieved the benefit of providing a more effective means of detecting epithelial cell markers by reducing contamination caused by the CD34+ cells.

(Office Action, page 9). Applicants respectfully disagree.

The Ts'o reference

The Ts'o reference discusses a "Method of Enriching Rare Cells". However, the Ts'o reference fails to discuss the elimination of CD34+ cells. One of ordinary skill in the art would not have been motivated to remove CD34+ cells. The Ts'o reference explicitly discusses using antibodies against many CD proteins, but does not refer to CD34. The Ts'o reference specifically discusses using antibodies against each of CD2, CD3, CD4, CD5, CD7, CD8, CD11a, CD11b, CD11c, CD14, CD15, CD16, CD19, CD20, CD28, CD36, CD42a, CD 43, CD44, CD45, CD45R, CD45RA, CD45RB, CD45RO, CD57, and CD61. In particular, the Ts'o reference states that "Antibodies targeted to human CD45, CD3, CD19, CD14, and CD36 are preferred." (Ts'o, Col. 12, lines 4-5). The Ts'o reference also has 14 examples, which only use antibodies that are targeted to human CD45, CD3, CD19, CD14, and/or CD36. The Ts'o reference does not motivate one of skill in the art to use antibodies directed against CD34 to remove CD34+ cells. Therefore, the Ts'o reference fails to teach all the elements of the invention.

The Palsson reference

The Palsson reference discusses a "Targeted System for Removing Tumor cells from Cell Populations". The Palsson reference states, "In particular, this invention relates to methods for specifically labeling and thereafter ***individually killing tumor cells*** with a focused high-energy beam such as a laser beam." (Palsson, Col. 1, lines 8-11, emphasis added). Palsson also describes the invention as providing "a targeted method of individually identifying and ***destroying contaminating tumor*** cells in a cell population."

(*Id.* Col. 1, lines 42-45, emphasis added). Therefore, one of ordinary skill in the art would read the Palsson reference as teaching methods to remove and kill tumor cells. One of skill in the art would not be motivated to apply the teachings Palsson in methods to detect tumor cells. Palsson teaches a method of killing tumor cells and ***away*** from methods that would require the tumor cells be present. One of skill in the art would not have been motivated to modify the Palsson reference to obtain the present invention because to detect a disseminated epithelial marker, the skilled artisan would need a tumor cell to be present, not destroy it as the Palsson reference teaches. Furthermore, although the Palsson reference discusses isolating CD34+ cells along with several other methods that have been used to isolate normal cells from tumor cells, Palsson states "Unfortunately, the whole population tumor purging methods...do not kill or remove all ***contaminating tumor cells*** from the harvested stem cell population." (*Id.*, Column 3, lines 21-24, emphasis added). Clearly, Palsson teaches away from the Ts'o reference and the present invention. A prior art reference may be considered to teach away when "a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27 F.3d 551, 553, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994). Thus, Palsson teaches away from eliminating CD34+ to detect a disseminated epithelial marker that are produced by tumor cells because Palsson describes the purpose of the reference is to eliminate the "contaminating tumor cells". There is no motivation to combine the Ts'o and Palsson references because the teachings of the references are completely opposite of one another.

However, even if there were motivation to combine the references one of ordinary skill in the art would not obtain the claimed invention when the references are taken as a whole. As discussed above claim 1 recites:

> A method of detecting the presence of a disseminated epithelial cell marker in a sample comprising the steps of
>
> a) eliminating CD34+ cells from the sample; and
>
> b) detecting the presence of mRNA that encodes the marker; wherein the marker is a differentiation specific antigen;

wherein said detection of said mRNA indicates the presence of a disseminated epithelial cell marker.

Thus, one of ordinary skill in the art using the present invention eliminates CD34+ cells from a sample and then detects the presence of mRNA that encodes a disseminated epithelial cell marker.

The references must be taken as a whole when ascertaining what they teach. Taken as a whole, the Palsson reference teaches how to destroy tumor cells not isolate them. Taken as a whole, the Ts'o reference teaches a method that does not eliminate CD34+ cells, but teaches how to isolate rare cells using antibodies against various proteins other than CD34. Thus, when the references are taken as a whole and combined, one would obtain an invention that isolates rare cells (Ts'o reference) and then destroys them (Palsson reference). Therefore, a combination of the Ts'o reference and the Palsson reference would create an invention that destroys tumor cells and, accordingly, prevent the detection of a disseminated epithelial marker thereby destroying the present invention.. Accordingly, the rejection for alleged obviousness is still improper, even if there were some motivation to combine the teachings of the cited references (and Applicants maintain that there is no such motivation), because a person of ordinary skill seeking to combine these references at the time of Applicants' invention would not have been led to any claimed subject matter.

The Office is respectfully reminded that when assessing whether or not a combination of references would have produced a claimed invention, one must consider the teaching of each reference as a ***whole*** without undue emphasis on those features that would support a finding of obviousness. *In re Wesslau*, 147 U.S.P.Q. 391 (C.C.P.A. 1965) (it is impermissible to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what the references fairly suggest to one of ordinary skill in the art). Consideration of the cited references as a whole for what they each fairly suggest, demonstrates that a person of ordinary skill seeking to combine them would not have produced any claimed invention.

The Palsson reference and the Ts'o reference also fail to render the present invention obvious because the references do not motivate one of skill in the art to remove

CD34+ cells to remove the high false positive rate that was associated with detection methods prior to the present invention. The present specification sates, "The high false positive rates appear to arise from illegitimate transcription of epithelial cell markers." (Specification, p.1, lines 24-25). Medical tests that have a high incidence of false positives can increase the cost of medical care as well as negatively impact an individual that is believed to be positive for a condition when in fact that individual is not. As the specification states:

> there is a need for methods of reducing the background signals caused by illegitimate transcription of cell markers used for the detection of cells that have migrated from their normal location in the body, including metastatic cancer cells. In particular there is a need to improve the accuracy and to decrease false-positive signals in highly sensitive, mRNA detection assays.

(Specification, page 5, lines 14-19). The present invention solved the problem of false positives (a long felt need) by identifying the main culprit, CD34+ cells. It is well settled that where the claimed invention solves a problem (false positives), the discovery of the source of the problem (CD34+ cells) and its solution (eliminating CD34+ cells) are considered to be part of the "invention as a whole" under 35 U.S.C. §103. *In re Kaslow*, 707 F.2d 1366, 217 U.S.P.Q. 1089 (Fed. Cir. 1983); *In re Nomiya*, 509 F.2d 566, 184 U.S.P.Q. 607 (C.C.P.A. 1975); and *In re Sponnoble*, 405 F.2d 578, 160 U.S.P.Q. 237 (C.C.P.A. 1979). Neither the Ts'o reference nor the Palsson reference, alone or in combination, claimed to solve the problem of false positives or identified a solution, and therefore, do not render any invention obvious.

Claims 6 and 41 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Ts'o *et al.* (U.S. Patent No. 5,962,237), in view of Palsson, B. (U.S. Patent No. 5,874,266) and in further view of Elliot (U.S. Patent No. 5,885,574). Applicants respectfully disagree.

Claims 14-15 and 46-47 stand rejected under 35 U.S.C. § 103 (a) as allegedly unpatentable over Ts'o *et al.* (U.S. Patent No. 5,962,237), in view of Palsson, B. (U.S. Patent No. 5,874,266) and in further view of Waldman *et al.* (Cancer Epidemiology, Biomarkers & Prevention (1998) 1:505-514). Applicants respectfully disagree.

As discussed above one of ordinary skill in the art would not have been motivated to combine the Ts'o reference and the Palsson reference. Furthermore, even if the references were combined, the result would not yield Applicants' invention for the reasons discussed above. Accordingly, since one of ordinary skill in the art would not have combine the Ts'o and Palsson references and even if the references were combined the result would not yield the claimed invention Claims 6, 14-15, 41, and 46-47 are also not obvious for the same reasons.

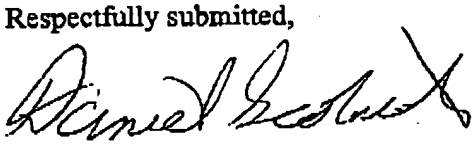
In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 103 be withdrawn.

Docket No.: TJU00014-100(TDT-ADV-006) **PATENT**
Serial No. 09/820,215 **Filed: March 27, 2001**

Conclusion

The examination of these claims and passage to allowance are respectfully requested. An early Notice of Allowance is therefore earnestly solicited. Applicants invite the Examiner to contact the undersigned at (215) 665-6928 to clarify any unresolved issues raised by this response.

Respectfully submitted,



Daniel M. Scolnick

Registration No. 52,201

Date: **July 15, 2005**
COZEN O'CONNOR, P.C.
1900 Market Street
Philadelphia, PA 19103-3508
Telephone: (215) 665-6928
Facsimile: (215) 701-2029